REMARKS

The present application is directed to a method for detecting the presence of a target nucleic acid sequence in a sample by amplifying the target to produce an amplification reaction product that includes a purine rich region, contacting the sample with a peptide nucleic acid able to bind to at least a portion of the target sequence and detecting the presence of triplex DNA structures. The application is also directed to a kit containing a peptide nucleic acid (PNA) sequence designed to form a triplex with a target sequence and a set of amplification primers that can amplify a sequence including the target sequence.

Upon entry of the amendment, Claims 1-2, 5-6, 8-12, 18-19 and 22-26 will be pending. Claims 20 and 21 have been cancelled without prejudice. Claims 1, 18 and 25 are currently amended. Support for the above amendments can be found in original Claims 1, 3 and cancelled Claim 20.

Objection to Specification

In the Office Action mailed May 5, 2006, the Examiner objected to the specification because the abstract recited the legal phraseology "said". Applicants have amended the Abstract to delete the term "said" as requested by the Examiner. For at least the foregoing reasons, withdrawal of the objection is respectfully requested.

Rejection Under 35 U.S.C. §102(b)

In the Office Action mailed May 5, 2006, the Examiner rejected Claims 25 and 26 under 35 U.S.C. §102(b) as being anticipated by Graham *et al.*, (WO 97/05280)(hereinafter "Graham"). Applicants respectfully submit that amendment to the claims overcome the rejection.

Claim 25 has been amended to recite a kit comprising bis-PNA that forms a PNA_2DNA triplex structure with the target nucleotide sequence. Additionally, Claim 25 has also been amended to recite a set of amplification primers contained within the kit that must be able to amplify a sequence comprising the target sequence in the presence of the bis-PNA. Applicants respectfully submit that Graham fails to teach a kit comprising bis-PNA for detecting the

presence of a target nucleic acid sequence in a sample. Accordingly, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102(b).

In the interest of advancing prosecution, applicants would like to comment also on the non-obviousness of the kit of Claims 25 and 26. Graham discloses a kit comprising a surface enhanced (resonance) Raman scattering ("SER(R)S")-active label bound to a SER(R)S-active surface and optionally attached to a target binding species such as a PNA probe designed to react with a target of interest (page 57, first full paragraph). In this context, it is taught in Graham that the PNA probe would "bind to DNA to form hybrids which are more stable than the corresponding DNA-DNA hybrids" (page 39, second paragraph). Graham also teaches that PNA "would be expected to be less acidic than the corresponding wild-type DNA or RNA sequence and would therefore show an increased affinity for a SER(R)S-active surface" (page 40, lines 1-4). Applicants respectfully submit that there is no motivation or suggestion to use **bis-PNA** in the kit disclosed in Graham for forming a PNA_2DNA triplex structure with the target nucleotide sequence, as recited in amended Claim 25.

Furthermore, there is no motivation or suggestion that amplification primers when present in the kit of Graham must be able to amplify the target sequence in the presence of bis-PNA complementary to the amplified sequence. For reasons discussed above, prior to the teachings of the present application, a person of ordinary skill in the art would not have expected such an amplification to succeed. Applicants respectfully submit that the kit of amended Claim 25 and dependent Claim 26 is non-obvious over Graham either alone or in combination with prior art previously cited by the Examiner.

Rejection Under 35 U.S.C. 103(a)

In the Office Action mailed May 5, 2006, the Examiner rejected Claims 1, 2, 5-6, 8-9, 12 and 22-24 under 35 U.S.C. § 103(a) as being obvious over Vary *et al.*, (U.S. Patent No. 5,800,984)(hereinafter "Vary") in view of Egholm *et al.*, (WO 96/02558 A1)(hereinafter "Egholm"). Applicants respectfully submit that amendment to the claims overcome the rejection.

Vary teaches a method for detecting a nucleic acid target sequence by formation of a triplex structure, however, Vary fails to teach or suggest the use of a **PNA** probe to form the triplex structure.

The deficiencies of Vary are not satisfied by Egholm for at least the following reasons. Egholm teaches novel PNAs such as bis-PNA that are "particularly useful for diagnostic uses, including the identification of certain sites in double stranded DNA, restriction enzyme sites, transcription inhibition, clamping to detect point mutations and for use in Hoogsteen strands in triplexing motif" (page 6, lines 25-30). The Examiner refers to the "Background of the Invention" section in Egholm that states "PNA binds both DNA and RNA to form PNA/DNA or PNA/RNA duplexes ... bound **with greater affinity** than corresponding DNA/DNA or DNA/RNA duplexes" (page 3, lines 15-18) (emphasis added). Egholm further teaches that PNAs have been used to detect point mutations in PCR-based assays, a technique known as "PCR clamping" (see page 5, lines 9-21). In PCR clamping, PNA is used to detect point mutations in a PCR-based assay by preferentially binding to target DNA comprising wild-type sequence and therefore **preventing PCR amplification** in the absence of a point mutation in the target sequence.

Applicants respectfully submit that the cited references **teach away** from using PNA probes complementary to a target sequence **during an amplification reaction** of the target sequence (as recited in amended Claim 1). Far from having a reasonable expectation of success, it would be more reasonable for one of ordinary skill in the art to deduce from the cited references that the stability of a triplex formed between the amplified target sequence and the PNA **would be so high that it would effectively clamp further amplification** of the product. Rather than being motivated to combine the cited references, applicants respectfully submit that one of ordinary skill in the art would consider it technically disadvantageous to use a PNA probe for a target sequence during amplification of that target sequence due to the **high affinity of PNA for DNA,** as noted by Egholm.

Indeed, corroborating evidence published in the scientific literature **after** the present invention was made confirmed that nucleic acid amplification **can** occur in the presence of a complementary PNA and this was considered to be highly surprising in view of the known

properties of PNA referred to by the Examiner. For example, applicants respectfully direct that Examiner to Wolffs *et al.* (2001; *BioTechniques* 31: 766-771; previously submitted) that used PNA conjugated to thiazole orange to form a "light-up" probe for use in real-time PCR and concluded that such PNA **"light-up probes do not inhibit DNA amplification, as might have been expected from PCR clamping studies"** (page 270, final paragraph) (emphasis added).

Contrary to the assertions of the Examiner, applicants submit, as supported by published technical evidence such as Wolffs *et al.*, that it would not have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Vary to include a PNA probe as taught by Egholm. Accordingly, applicants respectfully request withdrawal of the Examiner's rejection under 35 U.S.C. §103(a) of Vary in view of Egholm.

In the Office Action mailed May 5, 2006, the Examiner rejected Claims 10-11 and 18-21 under 35 U.S.C. § 103(a) as being obvious over Vary in view of Egholm (already of record) as applied to Claims 1-2, 5-6, 8-9, 12 and 22-24 above, and further in view of Graham. Applicants respectfully submit that amendment to the claims overcome the rejection.

Applicants respectfully submit that Claims 10 and 11 are non-obvious over the cited prior art by dependency on Claim 1. Claims 10 and 11 are indirectly dependent on Claim 1 and as such, incorporate all the limitations thereof. As discussed above, there is no motivation for one of ordinary skill in the art to combine the references of Vary and Egholm.

Additionally, Claim 18 has been amended to recite that the claimed method now requires that the amplification reaction occur in the presence of a PNA immobilized on a wave guide of an evanescent wave guide detector. For reasons discussed above, applicants respectfully submit that it would not have been obvious for a person of ordinary skill in the art at the time the invention was made to combine the cited references as suggested by the Examiner. Furthermore, Claim 19 is dependent on amended Claim 18 and is therefore also free of the prior art. Claims 20 and 21 are cancelled herein without prejudice.

Applicants respectfully submit that for a rejection under 35 U.S.C. §103(a) to be proper, each and every element of the claim must be disclosed in the combination of cited references and that there must be a **reasonable expectation of success**. As discussed above, applicants respectfully submit that the cited references **teach away** from using PNA probes

complementary to a target sequence **during an amplification reaction** of the target sequence (as recited in amended Claim 1). Applicants respectfully assert that one of ordinary skill in the art would therefore lack the motivation to make or use the claimed method in view of the cited art. For at least the foregoing reasons, withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

CONCLUSION

In light of the amendments and the above remarks, applicants are of the opinion that the Office Action has been completely responded to and that the application is now in condition for allowance. Such action is respectfully requested.

If the Examiner believes any informalities remain in the application that may be corrected by Examiner's Amendment, or there are any other issues that can be resolved by telephone interview, a telephone call to the undersigned attorney at (404) 815-6500 is respectfully requested.

No additional fees are believed due, however, the Commissioner is hereby authorized to charge any deficiencies that may be required, or credit any overpayment, to Deposit Account Number 11-0855.

Respectfully submitted,

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